REMARKS

Claims 1-13 remain pending in the present application.

Rejection under 35 U.S.C. 103 over Adachi et al. in view of Sheffield et al.

Claims 1-13 are rejected under 35 U.S.C. §103(a) as obvious over Adachi et al. in view of Sheffield et al. Applicants traverse this basis for rejection and respectfully request reconsideration and withdrawal thereof.

Adachi et al. is discussed at length in the present specification at page 5, lines 6-26 (identified as "Shinya et al."), wherein Applicants indicate that the authors administered Tranilast orally both pre- and post-operatively in a rat intraperitoneal adhesion model.

Adachi et al. fail to disclose or suggest "...locally administering a composition comprising a delivery vehicle containing Tranilast, or an analog thereof, directly onto said tissue surfaces at the surgical site..." as is required by claim 1.

The Examiner recognizes that Adachi et al. fail to disclose or suggest local administration of Tranilast directly onto tissue surfaces at sites subject to adhesion formation, and attempts to cure the deficiencies of Adachi et al. by citation of Sheffield et al., which discloses local administration of NSAID compounds to treat adhesions.

In formulating the reason for combining Adachi et al. and Sheffield et al., the Examiner concludes:

> Therefore, taking the teachings of Adachi and Sheffield, one having ordinary skill in the art at the time the invention was made would have reasonably expectation of success that topical or oral administration anti-adhesion composition of Adachi or Sheffield or the combined composition of Adachi and Sheffield would produce the expected inhibition of post surgical adhesion. (Office Action of November 27, 2009; page 4; emphasis added).

Applicants respectfully traverse the Examiner's conclusion that there would have been a reasonable expectation of success that a pharmaceutical compound known to be useful in oral administration (i.e. Tranilast) would be likewise useful for topical/local administration directly onto damaged tissue.

As discussed previously, Sheffield et al. is directed strictly to topical administration of NSAIDS for adhesion prevention. NDSAIDS are a completely different class of pharmaceuticals as compared to Tranilast, with completely different biological activities as compared to Tranilast. As such, one skilled in the art would not consider Tranilast a substitute for NSAIDS, whether administered orally or topically.

Further, the Examiner's proposal that because a particular pharmaceutical is known to have a particular efficacy through oral administration, that it would necessarily have similar efficacy if administered topically is scientifically questionable at best and certainly in the realm of the unpredictable.

> The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." KSR, 550 U.S. at ___, 82 USPQ2d at 1396. If any

> of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. **MPEP 2143 (A)** (Emphasis added).
>
> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007). **MPEP 2143.01 (III).**

As the Examiner is well-aware, oral administration routes the pharmaceutical through the alimentary system, wherein it is acted upon by multiple body chemistries which often result in modification of the original pharmaceutical compound into various derivatives and/or reaction products, which are the efficacious compounds. If administered topically, there is no guarantee that similar chemistries will occur, and therefore topical efficacy cannot be predicted, or even reasonably expected.

At page 5 of the outstanding Office Action, the Examiner explains:

> Applicant argues that Sheffield is directed strictly to topical administration of NSAID for adhesion prevention and that NSAIDs are completely different class of pharmaceuticals as compared to tranilast so that one skilled in the art would not consider tranilast a substitute for NSAIDs whether the administration is topical or oral.
>
> Applicant's arguments are not persuasive. The rejection is not one where substitution of one drug for another is advocated. Rather, because it is known in the art to topically administer compositions directly on to a surgical site for treating or preventing adhesion formation, it would be reasonable to expect that the topical or local administration of tranilast composition would be expected to effectively inhibit post adhesion formation. Further, the comprising language of the claims is open so that the combined composition of Adachi and Sheffield would also meet the limitation of the claimed composition topically applied to inhibit adhesion. (Emphasis added).

Applicants respectfully traverse the Examiner's findings. Initially, what the Examiner is suggesting is the epitome of a substitution rejection; i.e. that since Sheffield et al. disclose that NSAIDs can be topically administered to treat post-operative adhesion, it would instead be obvious to topically administer a different drug, in this case Tranilast, according to Adachi et al.

In the alternative, the Examiner's case rests on the obviousness of applying Tranilast per Adachi et al., in the manner disclosed by Sheffield et al. In either situation, substitution of either the drugs or administration methods is required.

It goes without saying that it is known in the art to topically administer various agents for adhesion inhibition. That is not the issue here. The issue is whether one skilled in the art would have chosen to topically administer a drug (Tranilast) suggested to be effective for adhesion inhibition *via* oral administration. In this regard, Applicants reiterate their discussion regarding the chemistry of the alimentary tract, set forth above. One of skill in the art would have had no expectation of success in merely varying the method of delivery of Tranilast, regardless of the Sheffield et al. disclosure. The predictability of efficacy is lacking. See *KSR*, Id.

In assessing predictability, it is a settled tenet of patent law that:

> Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). **MPEP 2143.02 (II).** (Emphasis added).

Indeed, Applicants provide data which demonstrates the lack of efficacy of Tranilast in reducing adhesions *via* oral administration, directly in contrast to the

teachings of Adachi et al. These data are reproduced below for the Examiner's convenience.

Example 3: Sidewall Model Evaluation of Tranilast: Oral Systemic Versus Local Delivery

Groups of animals received either oral dosing, or local delivery of Tranilast, or placebo control. In the animals that received local delivery, a single pump, filled with placebo (70% Polyethylene glycol 400, 20% Tween 80, 10% N,N-dimethylacetamide (DMAC)), or Tranilast (6.25 mg/ml), at 10 microliter/hour over 7 days starting with the day of surgery, was placed in the subcutaneous space. Certain animals received oral dosing (approximately 60 mg/kg). Oral dosing was either pre-operatively (once a day for the 5 days prior to surgery, with the last dose given 2 hours prior to surgery) or, in one group, pre- and post-operatively (from day 2 through day 21 post-surgery). For further clarification, the treatment groups are shown below. (Specification, page 33, line 5, bridging to page 34; emphasis added).

The treatment groups were:

Group	Pre-op Oral	Post-op Oral	Pump (6.25 mg/ml)
1	0	0	Placebo
2	0	0	Tranilast
3	Tranilast	Tranilast	None
4	Tranilast	0	Placebo
5	Tranilast	0	Tranilast

The results from this study are shown in Tables 12-16. There were reductions in the area of adhesion formation in all groups that received local delivery of Tranilast (Tables 13 and 16). Oral Tranilast alone did not reduce the area of adhesion formation (Tables 14 and 15). (Page 34, lines 12-17; emphasis added).

Table 12. Adhesion Scores in Placebo Treated Animals

Animal Number	Adhesion Area Percentage	Adhesion Tenacity
1	100	2
2	100	3
3	100	3
4	100	3
5	100	2
6	100	3
7	100	3

Table 14. Adhesion Scores in Animals Treated with 60 mg/kg Tranilast (5 Days Pre-operatively and 21 days Post-operatively)

Animal Number	Adhesion Area Percentage	Adhesion Tenacity
1	100	2
2	100	2
3	100	2
4	100	2
5	100	2
6	Died	
7	100	2

Table 15. Adhesion Scores in Animals Treated with 60 mg/kg Tranilast (5 Days Pre-Operatively) and Placebo Topically

Animal Number	Adhesion Area Percentage	Adhesion Tenacity
1	100	2
2	100	1
3	100	2

4	100	1
5	100	2
6	Died	
7	100	2

As described in the examples, Tranilast was shown to be efficacious when delivered to the site via a local administrative route. When delivered via a systemic route, no efficacy was seen. Hence, only local delivery is effective in reducing post-operative adhesions. (Pages 35-37; emphasis added).

Clearly this data calls into question the enablement of Adachi et al., and further demonstrates that absolutely no predictability of the efficacy of Tranilast on topical administration can be deduced from its lack of efficacy on oral administration.

As such, the Examiner's proposed modification amounts to no more than an obvious-to-try rationale for rejection, unsupported by any prior art, or for that matter any scientific reasoning. The skilled artisan would have had no reasonable expectation of success in inhibiting adhesions via topical application of Tranilast, derivable from the cited references.

Withdrawal of the rejection is requested on this basis alone.

In view of the foregoing, it is respectfully submitted that the present claims are in condition for allowance. Prompt notification of allowance is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 50-2478(13792).

If the Examiner has any questions or wishes to discuss this application,

the Examiner is invited to contact the undersigned representative at the number set forth below.

Respectfully submitted,

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